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THERE are very few diseases that have excited more interest in the medical world within the past decade than myxedema, and there are very few discoveries in the domain of therapeutics that have been so brilliant as the treatment of this disease by thyroid extract. The history of the discovery of the remedy reads like a novel. The clinical features of the disease were carefully determined by a committee of the Clinical Society of London in 1889, but its origin remained unknown. The observations of surgeons, that a similar affection followed the removal of goiter, gave the first clue to the origin of the clinical symptoms. The brilliant researches of Horsley, by means of physiologic experiment, determined the function of the thyroid gland in maintaining the body-temperature and the nutrition of various parts of the system, and proved that the absence of the gland caused the symptoms of myxedema. Finally, the idea developed of transferring to the human body the thyroid glands of animals, either by direct transplantation (Horsley



and Kocher) or by subcutaneous injection (Murray) or by ordinary administration by the mouth (MacKenzie), for the purpose of removing the symptoms of myxedema, which were due to the absence of this substance from the blood. The success of this method completed the history of the affection.

Those who have seen the very distressing physical and mental symptoms occurring in myxedema rapidly and progressively disappear under the administration of thyroid extract, until the patients are restored to perfect health, cannot but be impressed by the wonderful effect that the presence of this active principle in the blood has had. It has been my fortune to watch this transformation from a state of disease to a state of health in fourteen adults. The histories of several of these cases have been already published by myself<sup>1</sup> and by others.<sup>2</sup>

My object in reporting another case at this time is to call attention to certain features of myxedema that closely resemble the symptoms of chronic nephritis and to emphasize the importance of the distinction between these two diseases. This can hardly be exaggerated, for many of the cases of myxedema that are now cured had been considered cases of nephritis of an incurable nature, a mistake easily accounted for when we consider that the presence of albumin and of casts in the urine, together with an appearance of general edematous

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<sup>1</sup> Transactions of the Association of American Physicians, 1893, vol. viii, p. 361, three cases.

<sup>2</sup> Dr. George W. Crary, American Journal of the Medical Sciences, April, 1894, two cases; also, Dr. S. J. Meltzer, N. Y. Medicin. Monatschr., April, 1894, one case.



swelling of the body, is uniformly noticed in this disease. After recording the history of the following case an attempt will be made to indicate the chief points of differential diagnosis.

G. W. H., aged forty-five, had been perfectly well until the early part of 1892, when without any known cause he began to suffer from a gradually increasing swelling of the hands, face, nose, mouth, and tongue, which was accompanied by the appearance of a yellow pigmentation upon the hands and face and a decided thinning of the hair. This condition gradually increased during the summer, and he found that he was unable to perspire, no matter how hot the weather. During the autumn, in addition to the symptoms mentioned, he noticed that his teeth were loose, that the gums were sore, bled quite frequently, and seemed to be soft; that the swelling of the mouth and tongue had become so great as to materially change the character of his voice, making talking monotonous and decidedly slower; and that the swelling also interfered with breathing easily through the nose, so that he kept his mouth open, and at times had some difficulty in swallowing. As winter came on he suffered more from the cold than he had ever done previously. The swelling had by this time gradually extended over the entire body, giving him the appearance of being rather fleshy, so that his tailor had to let out his clothing an inch-and-a-half about the waist. The appearance of his face during this time had progressively altered, and presented certain peculiarities; the hair of the head had become coarse and rather thin; the hair of his moustache was also coarser than formerly and had become bristly, so that it could not be kept smooth as formerly; the skin of the entire face was thickened and pig-

mented ; this was particularly noticeable about the forehead, where deep wrinkles appeared, and around the eyes (which could hardly be opened to their full extent), and about the mouth, where the lips were thick and heavy ; there was a peculiar elevation of the external corner of the eyebrows in the effort to

FIG. 1.



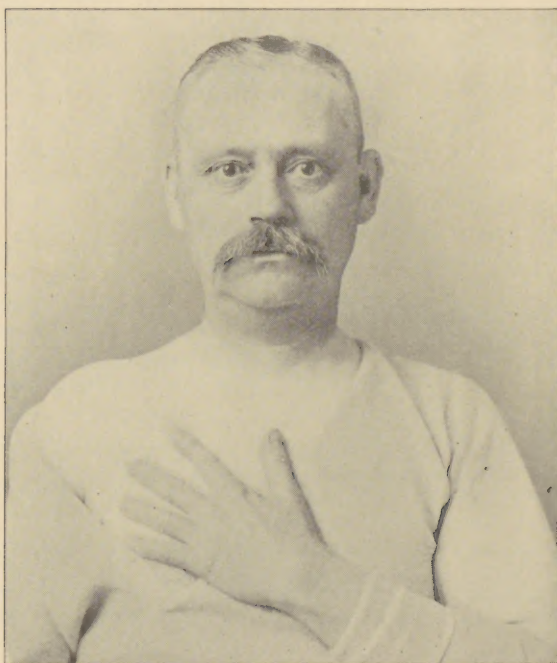
open the eyes ; and a thickening of the face at the side of the nose was very perceptible. His extremities were also swollen and pigmented ; the skin all over the body was dry and scaly. His friends had noticed the slowness of his speech and the peculiar

thickness of utterance. Many of these characters are well shown in his photograph (Fig. 1), which was taken in May, 1894.

The diagnosis of myxedema was made by his physician in San Francisco, in September, 1893, and the thyroid treatment had been begun about that time and kept up until May, 1894, when I first saw him. Whether the preparation used had been defective or imperfectly prepared I do not know; but his improvement had been slow, though perceptible, during the winter. When I saw him in May I observed, in addition to the symptoms and appearance already noticed, very marked supra-clavicular swellings, slightly subnormal temperature, a marked slowness mentally, attended by a tendency at times to feelings of depression and the characteristic speech of myxedema. He had not had hallucinations, and the mental hebetude was less than I have seen in other cases. Examination of the urine showed the presence of small amounts of albumin and a few large and small hyaline casts; his pulse was slow—60—and rather hard and irregular. He felt himself unfitted to do business by reason of his condition, and though not suffering any pain, was decidedly uncomfortable and distressed at his state. He was placed immediately upon the 5-grain tabloids of thyroid extract prepared by Burroughs, Welcome & Co., of London, these having proved to be the most active and least disagreeable of all the preparations of thyroid which I have employed. He was given three a day, but this number caused a rise of temperature and a rapid action of the heart, and hence the dose was reduced to two daily. During the following month his progress was very rapid, and the change in his appearance was extraordinary. All the symptoms gradually disappeared, excepting the pigmentation of the face

and hands; the swelling subsided everywhere, so that at the end of the month he was wearing a number fifteen collar instead of a seventeen, and all his clothing was too loose; his facial expression had altered

Fig. 2.



greatly for the better, and was almost like that shown in Fig. 2, a photograph taken in September, 1894. This photograph shows the remarkable change in the general appearance. There has been a correspond-



ing change in his general feelings and in his mental capacity ; he is now able to do business of an active kind with his usual ability. His voice has become natural, he has no disturbance in swallowing or breathing, and, in fact, is in his usual state of health. Within a month of the beginning of treatment the albumin and casts had entirely disappeared from the urine, and there was present no evidence of any disease of the kidneys. The only unfavorable symptom that has been noticed during the course of treatment has been a marked effect of the thyroid extract upon his heart ; the pulse has been persistently rapid and irregular, and he has suffered from a sense of weight and distress in the region of the heart and dyspnea on any exertion. This had never been present until the thyroid extract was used. It increased to a point of great distress when the thyroid was increased beyond fifteen grains daily, and it became less when the thyroid was stopped. He finds it necessary to take three grains of the extract, however, as, if he stops for more than two weeks, his symptoms begin to return. The distress did not appear to be very much affected by heart-stimulants and by strychnin, which were administered from time to time with a view of correcting this depressant action of the remedy. It is, of course, necessary for him to continue indefinitely the use of the thyroid extract, as this supplies to his blood an element, the absence of which produces all his symptoms.

The general appearance of patients suffering from myxedema—their cachectic look, yellowish color, and swollen faces and extremities—suggests to the ordinary observer a condition of nephritis. When the history of gastric distress and indigestion, of general malaise and fatigue on slight exertion, of headaches and mental incapacity, of insomnia, and

of general edema is heard, the first suspicion is likely to be strengthened. And when the examination of the urine shows albumin and hyaline casts it seems as if the diagnosis of chronic nephritis was perfectly certain. I have made this mistake myself in two cases, and have known it to be made by some of the most accurate diagnosticians in this country before myxedema became as familiar as it is at present. Yet unless a physician has examined and studied patients suffering from myxedema he may be quite liable to this error, and hence I desire to call particular attention to the points of differential diagnosis between myxedema and chronic nephritis.

In the first place, we need to remember that edema occurs under two forms of nephritis in very different degrees. 1. In the acute form of nephritis with scanty urine of high specific gravity, large amounts of albumin, and many casts, when all the general symptoms are intense and convulsions are imminent, the edema is usually extreme. The face, body, arms, and especially the legs, are much swollen and pit upon pressure, and it is evident that the edema is governed not a little by gravitation, for it is more extreme in the dependent parts of the body—the feet, ankles, and legs, if the patient is up and about; in the back, if he is in bed. Now in myxedema, even when the swelling is very marked, it has characteristics entirely different from those just described. It affects the forehead as well as the face, it is as intense in the upper eyelid as in the lower, it never fails to cause a thickening of the bridge of the nose, and of the lips and tongue. In all these

respects it differs from the edema of nephritis. It is more intense over the masseter muscles and in the supra-clavicular spaces than anywhere else, forming pads of soft tissue almost like lipomata. These spaces are not often swollen in nephritis. It affects the surface of the body quite uniformly, but is more noticeable on the abdomen than on the back, no matter what the position habitually assumed. Nor is it all affected by gravitation. The legs are uniformly swollen all the way down, not particularly about the ankles or tibia, and the hands and arms are quite as much affected as the feet. The very soft parts about the genitals are not excessively swollen, as in nephritis. In fact, as a rule, the extreme swelling in myxedema is usually in the face and neck, and not in the feet and legs—just the reverse of the condition in nephritis. Finally, in myxedema there is no pitting upon pressure, and no evidence that fluid beneath the skin can be displaced by manipulation. Aside, then, from the fact that the slow onset and gradual course of a case of myxedema contrast markedly with the acute and severe symptoms of acute nephritis, it is possible by an examination of the edema to differentiate between these two diseases.

2. But there is another form of nephritis that produces edema, viz., chronic nephritis with contracted kidneys, hypertrophied heart, and increased arterial tension. This is the form with which myxedema is most frequently confounded. An excessive amount of urine of low specific gravity, scanty traces of albumin, and a few hyaline casts are commonly observed in both diseases. In both the

symptoms are of slow progress; in both cerebral and gastric symptoms are prominent; and in both the pallor and yellowish tint of the skin are known to occur. Here again it is to be remembered that the edema is entirely different in the two diseases. In chronic nephritis the edema is not very marked, but when it is present it is uniformly noticed about the ankles after standing, or along the tibiæ; it never affects the hands and arms; when it appears in the face it is under the eyelids, never on the forehead, lips, or tongue. In a word, it is located in dependent parts of the body, and is determined by gravitation, or it appears in the parts where the normal tissues are loose and where the subcutaneous tissue has spaces in which fluid can easily collect. The description already given of myxedematous swellings contrasts in every point with these particulars. Hence, it is evident that in the second form of nephritis, in which edema occurs, the examination of the patient should suffice to detect the differences from myxedema.

But there are many other points of differentiation. I have alluded to the color of the skin and the pallor as common to the two diseases. In myxedema the skin is remarkably dry and usually in a state of active desquamation. The patients have the appearance of having been recently powdered, and by rubbing the surface gently, scaly white particles of epithelium are easily brushed off. This condition of the skin is certainly not common, if it occurs at all in nephritis.

Again, in myxedema there is no suggestion that the skin is unduly stretched, as in ordinary edema,



and it is not thin, and smooth, and flossy. While, as a rule, in myxedema the color of the skin is yellowish-white, all observers have noticed a bright-red blush over the cheek-bones, which sometimes gives the impression that the patients, who are usually women, have been rouged. This high color is not seen in nephritis.

The entire absence of perspiration in myxedema, the inability of the patient to get into a perspiration by any exertion or exposure to heat is another symptom not particularly noticed in nephritis.

The condition of the hair—thin, bristly, coarse, and dry—is characteristic of myxedema. Inquiry will also usually elicit the fact that from all parts of the body where hair appears there has been a marked falling of it, so that the patient may be noticeably lacking in it; in the axillæ or about the genitals, as well as on the head. In nephritis the growth of hair is not affected.

Lastly, it is to be remembered that the thyroid secretion has an important function in regulating the body temperature, and that in myxedema there is a uniform depression of temperature, the thermometer registering only  $97^{\circ}$  or  $97.5^{\circ}$  in the mouth. Such a condition is not observed in nephritis or in any other disease. It is accompanied by a subjective feeling of cold, which is one of the most annoying symptoms to those who live in the North. It is one of the immediate results of the thyroid treatment that the temperature rises under the use of the extract. I have tried the extract in other diseases, and have never seen it produce this effect excepting in cases of myxedema. In cases of

akromegaly, in which it seems to have a beneficial effect, it does not cause any elevation of temperature; and in a case of megaloccephaly, in which it was very thoroughly tried to the extent of ten tablets daily, it had no such effect. It is by watching the temperature and the pulse that the proper dosage of the extract is to be determined in each case. It is better to begin with small doses, one tabloid (5 grains) daily, or 10 drops of the glycerin extract of Dr. Crary<sup>1</sup> daily, and gradually increase the amount, than to give large quantities and cause disagreeable symptoms. In the case here reported the cardiac distress caused by the extract was very marked, and could not be counteracted.

While in the case reported there were no mental symptoms present, I think it is right to call attention to the fact that a considerable proportion of the cases of myxedema suffer from hallucinations, from great mental depression, from defects of memory, and from decided inability to use the mind. Three out of the thirteen cases that I have seen were brought to me because of the mental symptoms. The type of derangement which is present in myxedema is somewhat different from that ordinarily seen in mental diseases. While there is a depression and a decided melancholic tendency, there are very rarely any delusions, and never the typical facial expression of melancholia; nor are there intercurrent periods of mental depression and self-accusation which often occur in melancholia. The patients do not wake early in the morning with the intense depression that is seen in that disease. In melan-

<sup>1</sup> New York Medical Record, June 17, 1893.

cholia hallucinations are exceedingly infrequent, while almost all myxedematous patients when affected mentally will describe hallucinations of sight and, sometimes, of hearing, occurring frequently at night; animals and faces are seen, and voices are heard, yet, as a rule, these hallucinations are recognized as products of the mind; they are not firmly believed in, and they do not become the cause for excitement as in hallucinatory insanity.

The prevailing mental tendency in myxedema is toward a demented condition; the patients are stupid, dull, sit listless, doing nothing, prefer to be left alone, take no interest in their surroundings, and appear to be lacking in all spontaneous mental processes; yet even this form of dementia differs decidedly from the primary dementia or the terminal dementia of insomnia, for the patients can be aroused to thought, show few defects when excited to mental action, and none of the incoherence of speech which betrays a mind permanently shattered. The entire disappearance of all these mental symptoms is one of the gratifying results of the treatment with thyroid extract. The three patients to whom I have alluded remain in a state of mental as well as physical health so long as they continue to use the extract. It is not at all improbable that a careful search in the asylums of this country would result in the discovery of a number of cases of myxedema now supposed to be instances of chronic dementia, but really capable of cure.











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